CLAIMS

- 1. A function inhibitor of an effector cell, which comprises a CCR5 antagonist.
- 2. The function inhibitor of an effector cell according to claim 1, wherein the function is cell migration, cell proliferation or cell activation.
- 3. The function inhibitor of an effector cell according to claim 1, wherein the effector cell is a CCR5-positive effector cell.
- 4. The function inhibitor of an effector cell according to claim 1, which is an agent for prevention and/or treatment of a disease caused by effector cell function.
- 5. The function inhibitor of an effector cell according to claim 1, which is an agent for prevention and/or treatment of a T cell-mediated disease.
- 6. The function inhibitor of an effector cell according to claim 1, which is an agent for prevention and/or treatment of a myeloid cell-mediated disease.
- 7. The function inhibitor of an effector cell according to claim 5, wherein the T cell-mediated disease is transplant rejection, autoimmune disease, allergic disease or ischemic disease.
- 8. The function inhibitor of an effector cell according to claim 6, wherein the myeloid cell-mediated disease is cancer or cancer metastasis.

- 9. The function inhibitor of an effector cell according to claim 1, wherein the CCR5 antagonist is a non-peptide substance.
- 10. The function inhibitor of an effector cell according to claim 1, wherein the CCR5 antagonist is a compound of formula (I)

$$R^{1}-N \xrightarrow{N} \xrightarrow{N} R^{3} \qquad (I)$$

$$Q \xrightarrow{R^{5}}$$

wherein R^1 represents (1) a hydrogen atom, (2) C1-18 alkyl, (3) C2-18 alkenyl, (4) C2-18 alkynyl, (5) -COR⁶, (6) -CONR⁷R⁸, (7) -COOR⁹, (8) -SO₂R¹⁰,

- (9) -COCOOR¹¹, (10) -CONR¹²COR¹³, (11) Cyc1 or (12) C1-18 alkyl, C2-18 alkenyl or C2-18 alkynyl substituted with 1-5 substituent(s) selected from (a) halogen,
- (b) $-CONR^7R^8$, (c) $-COOR^9$, (d) $-OR^{14}$, (e) $-SR^{15}$, (f) $-NR^{16}R^{17}$, (g) $-NR^{18}COR^{19}$,
- (h) -SO₂NR²⁰R²¹, (i) -OCOR²², (j) -NR²³SO₂R²⁴, (k) -NR²⁵COOR²⁶,
- (1) $-NR^{27}CONR^{28}R^{29}$, (m) Cyc1, (n) keto and (o) $-N(SO_2R^{24})_2$;

R⁶-R⁹, R¹¹-R²¹, R²³, R²⁵ and R²⁷-R²⁹ each independently represents (1) a hydrogen atom, (2) C1-8 alkyl, (3) C2-8 alkenyl, (4) C2-8 alkynyl, (5) Cyc1 or (6) C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted with 1-5 substituent(s) selected from (a) Cyc1, (b) halogen, (c) -OR³⁰, (d) -SR³¹, (e) -NR³²R³³, (f) -COOR³⁴, (g) -CONR³⁵R³⁶, (h) -NR³⁷COR³⁸, (i) -NR³⁹SO₂R⁴⁰ and (j) -N(SO₂R⁴⁰)₂, or

R⁷ and R⁸, R²⁰ and R²¹, or R²⁸ and R²⁹ are taken together to represent (1) C2-6 alkylene, (2) -(C2-6 alkylene)-O-(C2-6 alkylene)-, (3) -(C2-6 alkylene)-S-(C2-6 alkylene)- or (4) -(C2-6 alkylene)-NR¹⁹⁵-(C2-6 alkylene)-, wherein R¹⁹⁵ is a hydrogen atom, C1-8 alkyl, phenyl, or C1-8 alkyl substituted with phenyl;

 R^{10} , R^{22} , R^{24} and R^{26} each independently represents (1) C1-8 alkyl, (2) C2-8 alkenyl, (3) C2-8 alkynyl, (4) Cyc1 or (5) C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted with 1-5 substituent(s) selected from (a) Cyc1, (b) halogen, (c) \cdot OR³⁰, (d) \cdot SR³¹, (e) \cdot NR³²R³³, (f) \cdot COOR³⁴, (g) \cdot CONR³⁵R³⁶, (h) \cdot NR³⁷COR³⁸, (i) \cdot NR³⁹SO₂R⁴⁰ and (j) \cdot N(SO₂R⁴⁰)₂;

R³⁰-R³⁷ and R³⁹ each independently represents a hydrogen atom, C1-8 alkyl, Cycl or C1-8 alkyl substituted with Cycl, or

R³⁵ and R³⁶ are taken together to represent (1) C2-6 alkylene, (2) -(C2-6 alkylene)-O-(C2-6 alkylene)-, (3) -(C2-6 alkylene)-S-(C2-6 alkylene)- or (4) -(C2-6 alkylene)-NR¹⁹⁶-(C2-6 alkylene)-, wherein R¹⁹⁶ represents a hydrogen atom, C1-8 alkyl, phenyl or C1-8 alkyl substituted with phenyl;

R³⁸ and R⁴⁰ each independently represents C1-8 alkyl, Cyc1 or C1-8 alkyl substituted with Cyc1;

Cycl represents a C3-15 mono-, bi- or tri-(fused or spiro)carbocyclic ring or a 3-15 membered mono-, bi- or tri-(fused or spiro)cyclic hetero ring containing 1-4 nitrogen atom(s), 1-3 oxygen atom(s) and/or 1-3 sulfur atom(s), and Cycl may be substituted with 1-5 of R⁵¹;

R⁵¹ represents (1) C1-8 alkyl, (2) C2-8 alkenyl, (3) C2-8 alkynyl, (4) halogen, (5) nitro, (6) trifluoromethyl, (7) trifluoromethoxy, (8) nitrile, (9) keto, (10) Cyc2, (11) -OR⁵², (12) -SR⁵³, (13) -NR⁵⁴R⁵⁵, (14) -COOR⁵⁶, (15) -CONR⁵⁷R⁵⁸, (16) -NR⁵⁹COR⁶⁰, (17) -SO₂NR⁶¹R⁶², (18) -OCOR⁶³, (19) -NR⁶⁴SO₂R⁶⁵, (20) -NR⁶⁶COOR⁶⁷, (21) -NR⁶⁸CONR⁶⁹R⁷⁰, (22) -B(OR⁷¹)₂, (23) -SO₂R⁷², (24) -N(SO₂R⁷²)₂, or (25) C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted with 1-5 substituent(s) selected from (a) halogen, (b) Cyc2, (c) -OR⁵², (d) -SR⁵³, (e) -NR⁵⁴R⁵⁵, (f) -COOR⁵⁶, (g) -CONR⁵⁷R⁵⁸, (h) -NR⁵⁹COR⁶⁰, (i) -SO₂NR⁶¹R⁶², (j) -OCOR⁶³,

(k) $-NR^{64}SO_2R^{65}$, (l) $-NR^{66}COOR^{67}$, (m) $-NR^{68}CONR^{69}R^{70}$, (n) $-B(OR^{71})_2$, (o) $-SO_2R^{72}$ and (p) $-N(SO_2R^{72})_2$;

R⁵²-R⁶², R⁶⁴, R⁶⁶ and R⁶⁸-R⁷¹ each independently represents (1) a hydrogen atom, (2) C1-8 alkyl, (3) C2-8 alkenyl, (4) C2-8 alkynyl, (5) Cyc2 or (6) C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted with Cyc2, -OR⁷³, -COOR⁷⁴ or -NR⁷⁵R⁷⁶, or

R⁵⁷ and R⁵⁸, R⁶¹ and R⁶², or R⁶⁹ and R⁷⁰ are taken together to represent (1) C2-6 alkylene, (2) -(C2-6 alkylene)-O-(C2-6 alkylene)-, (3) -(C2-6 alkylene)-S-(C2-6 alkylene)- or (4) -(C2-6 alkylene)-NR¹⁹⁷-(C2-6 alkylene)-, wherein R¹⁹⁷ represents a hydrogen atom, C1-8 alkyl, phenyl or C1-8 alkyl substituted with phenyl;

R⁶³, R⁶⁵, R⁶⁷ and R⁷² each independently represents (1) C1-8 alkyl, (2) C2-8 alkenyl, (3) C2-8 alkynyl, (4) Cyc2 or (5) C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted with Cyc2, -OR⁷³, -COOR⁷⁴ or -NR⁷⁵R⁷⁶;

R⁷³-R⁷⁶ each independently represents a hydrogen atom, C1-8 alkyl, Cyc2 or C1-8 alkyl substituted with Cyc2;

Cyc2 has the same meaning as Cyc1, and Cyc2 may be substituted with 1-5 of R⁷⁷;

R⁷⁷ represents (1) C1-8 alkyl, (2) halogen, (3) nitro, (4) trifluoromethyl, (5) trifluoromethoxy, (6) nitrile, (7) -OR⁷⁸, (8) -NR⁷⁹R⁸⁰, (9) -COOR⁸¹, (10) -SR⁸², (11) -CONR⁸³R⁸⁴, (12) C2-8 alkenyl, (13) C2-8 alkynyl, (14) keto, (15) Cyc6, (16) -NR¹⁶¹COR¹⁶², (17) -SO₂NR¹⁶³R¹⁶⁴, (18) -OCOR¹⁶⁵, (19) -NR¹⁶⁶SO₂R¹⁶⁷, (20) -NR¹⁶⁸COOR¹⁶⁹, (21) -NR¹⁷⁰CONR¹⁷¹R¹⁷², (22) -SO₂R¹⁷³, (23) -N(SO₂R¹⁶⁷)₂ or (24) C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted with 1-5 substituent(s) selected from (a) halogen, (b) -OR⁷⁸, (c) -NR⁷⁹R⁸⁰, (d) -COOR⁸¹, (e) -SR⁸², (f) -CONR⁸³R⁸⁴, (g) keto, (h) Cyc6, (i) -NR¹⁶¹COR¹⁶², (j) -SO₂NR¹⁶³R¹⁶⁴, (k) -OCOR¹⁶⁵, (l) -NR¹⁶⁶SO₂R¹⁶⁷, (m) -NR¹⁶⁸COOR¹⁶⁹, (n) -NR¹⁷⁰CONR¹⁷¹R¹⁷², (o) -SO₂R¹⁷³, and (p) -N(SO₂R¹⁶⁷)₂;

R⁷⁸-R⁸⁴, R¹⁶¹-R¹⁶⁴, R¹⁶⁶, R¹⁶⁸ and R¹⁷⁰-R¹⁷² each independently represents (a) a hydrogen atom, (b) C1-8 alkyl, (c) C2-8 alkenyl, (d) C2-8 alkynyl, (e) Cyc6, (f) C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted with Cyc6, -OR¹⁷⁴, -COOR¹⁷⁵, -NR¹⁷⁶R¹⁷⁷ or -CONR¹⁷⁸R¹⁷⁹, or

R⁸³ and R⁸⁴, R¹⁶³ and R¹⁶⁴, or R¹⁷¹ and R¹⁷² are taken together to represent

(1) C2-6 alkylene, (2) -(C2-6 alkylene)-O-(C2-6 alkylene)-, (3) -(C2-6 alkylene)-S-(C2-6 alkylene)- or (4) -(C2-6 alkylene)-NR¹⁹⁸-(C2-6 alkylene)-, wherein R¹⁹⁸ represents a hydrogen atom, C1-8 alkyl, phenyl or C1-8 alkyl substituted with phenyl;

R¹⁶⁵, R¹⁶⁷, R¹⁶⁹ and R¹⁷³ each independently represents (a) C1-8 alkyl, (b) C2-8 alkenyl, (c) C2-8 alkynyl, (d) Cyc6 or (e) C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted with Cyc6, -OR¹⁷⁴, -COOR¹⁷⁵, -NR¹⁷⁶R¹⁷⁷ or -CONR¹⁷⁸R¹⁷⁹;

R¹⁷⁴-R¹⁷⁷ each independently represents (1) a hydrogen atom, (2) C1-8 alkyl, (3) Cyc6 or (4) C1-8 alkyl substituted with Cyc6, or

R¹⁷⁸ and R¹⁷⁹ are taken together to represent (1) C2-6 alkylene, (2) -(C2-6 alkylene)-O-(C2-6 alkylene)-, (3) -(C2-6 alkylene)-S-(C2-6 alkylene)- or (4) -(C2-6 alkylene)-NR¹⁹⁹-(C2-6 alkylene)-, wherein R¹⁹⁹ represents a hydrogen atom, C1-8 alkyl, phenyl or C1-8 alkyl substituted with phenyl;

Cyc6 represents a C3-8 mono-carbocyclic ring or a 3-8 membered mono-cyclic hetero ring containing 1-4 nitrogen atom(s), 1-2 oxygen atom(s) and/or 1-2 sulfur atom(s), with the proviso that, Cyc6 may be substituted with 1-5 of R¹⁸⁰;

R¹⁸⁰ represents (1) C1-8 alkyl, (2) halogen, (3) nitro, (4) trifluoromethyl, (5) trifluoromethoxy, (6) nitrile, (7) -OR¹⁸¹, (8) -NR¹⁸²R¹⁸³, (9) -COOR¹⁸⁴, (10) -SR¹⁸⁵ or (11) -CONR¹⁸⁶R¹⁸⁷;

R¹⁸¹-R¹⁸⁷ each independently represents (1) a hydrogen atom, (2) C1-8 alkyl, (3) phenyl or (4) C1-8 alkyl substituted with phenyl, or

R¹⁸² and R¹⁸³, or R¹⁸⁶ and R¹⁸⁷ are taken together to represent (1) C2-6. alkylene, (2) -(C2-6 alkylene)-O-(C2-6 alkylene)-, (3) -(C2-6 alkylene)-S-(C2-6 alkylene)- or (4) -(C2-6 alkylene)-NR²⁰⁰-(C2-6 alkylene)-, wherein R²⁰⁰ represents a hydrogen atom, C1-8 alkyl, phenyl, C1-8 alkyl substituted with phenyl;

R² represents (1) a hydrogen atom, (2) C1-8 alkyl, (3) C2-8 alkenyl, (4) C2-8 alkynyl, (5) -OR⁹⁰, (6) Cyc3 or (7) C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted with 1-5 substituent(s) selected from (a) halogen, (b) -OR⁹⁰, (c) -SR⁹¹, (d) -NR⁹²R⁹³, (e) -COOR⁹⁴, (f) -CONR⁹⁵R⁹⁶, (g) -NR⁹⁷COR⁹⁸, (h) -SO₂NR⁹⁹R¹⁰⁰, (i) -OCOR¹⁰¹, (j) -NR¹⁰²SO₂R¹⁰³, (k) -NR¹⁰⁴COOR¹⁰⁵, (l) -NR¹⁰⁶CONR¹⁰⁷R¹⁰⁸, (m) Cyc3, (n) keto and (o) -N(SO₂R¹⁰³)₂;

R⁹⁰-R¹⁰⁰, R¹⁰², R¹⁰⁴ and R¹⁰⁶-R¹⁰⁸ each independently represents (1) a hydrogen atom, (2) C1-8 alkyl, (3) C2-8 alkenyl, (4) C2-8 alkynyl, (5) Cyc3 or (6) C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted with Cyc3, or

R⁹⁵ and R⁹⁶, R⁹⁹ and R¹⁰⁰, or R¹⁰⁷ and R¹⁰⁸ are taken together to represent (1) C2-6 alkylene, (2) -(C2-6 alkylene)-O-(C2-6 alkylene)-, (3) -(C2-6 alkylene)-S-(C2-6 alkylene)- or (4) -(C2-6 alkylene)-NR²⁰¹-(C2-6 alkylene)-, wherein R²⁰¹ is a hydrogen atom, C1-8 alkyl, phenyl or C1-8 alkyl substituted with phenyl;

R¹⁰¹, R¹⁰³ and R¹⁰⁵ are each independently (1) C1-8 alkyl, (2) C2-8 alkenyl, (3) C2-8 alkynyl or (4) Cyc3, or C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted with Cyc3;

Cyc3 has the same meaning as Cyc1, and Cyc3 may be substituted with 1-5 of R¹⁰⁹;

R¹⁰⁹ has the same meaning as R⁵¹;

R³ and R⁴ each independently represents (1) a hydrogen atom, (2) C1-8 alkyl, (3) C2-8 alkenyl, (4) C2-8 alkynyl, (5) -COOR¹²⁰, (6) -CONR¹²¹R¹²², (7) Cyc4 or (8) C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted with 1-5 substituent(s) selected from (a) halogen, (b) nitrile, (c) Cyc4, (d) -COOR¹²⁰, (e) -CONR¹²¹R¹²², (f) -OR¹²³, (g) -SR¹²⁴, (h) -NR¹²⁵R¹²⁶, (i) -NR¹²⁷COR¹²⁸, (j) -SO₂NR¹²⁹R¹³⁰, (k) -OCOR¹³¹, (l) -NR¹³²SO₂R¹³³, (m) -NR¹³⁴COOR¹³⁵, (n) -NR¹³⁶CONR¹³⁷R¹³⁸, (o) -S-SR¹³⁹, (p) -NHC(=NH)NHR¹⁴⁰, (q) keto, (r) -NR¹⁴⁵CONR¹⁴⁶COR¹⁴⁷ and (s) -N(SO₂R¹³³)₂; R¹²⁰-R¹³⁰, R¹³², R¹³⁴, R¹³⁶-R¹³⁸, R¹⁴⁵ and R¹⁴⁶ each independently represents (1) a hydrogen atom, (2) C1-8 alkyl, (3) C2-8 alkenyl, (4) C2-8 alkynyl, (5) Cyc4 or (6) C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted with Cyc4, halogen, -OR¹⁴⁸, -SR¹⁴⁹, -COOR¹⁵⁰ or -NHCOR¹⁴¹, or

R¹²¹ and R¹²², R¹²⁹ and R¹³⁰, or R¹³⁷ and R¹³⁸ are taken together to represent (1) C2-6 alkylene, (2) -(C2-6 alkylene)-O-(C2-6 alkylene)-, (3) -(C2-6 alkylene)-S-(C2-6 alkylene)- or (4) -(C2-6 alkylene)-NR²⁰¹-(C2-6 alkylene)-, wherein R²⁰¹ represents a hydrogen atom, C1-8 alkyl, phenyl, C1-8 alkyl substituted with phenyl;

R¹³¹, R¹³³, R¹³⁵, R¹³⁹ and R¹⁴⁷ each independently represents (1) C1-8 alkyl, (2) C2-8 alkenyl, (3) C2-8 alkynyl, (4) Cyc4 or (5) C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted with Cyc4, halogen, -OR¹⁴⁸, -SR¹⁴⁹, -COOR¹⁵⁰ or -NHCOR¹⁴¹;

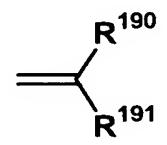
R¹⁴⁰ represents a hydrogen atom, -COOR¹⁴² or -SO₂R¹⁴³;

R¹⁴¹-R¹⁴³ each independently represents (1) C1-8 alkyl, (2) C2-8 alkenyl, (3) C2-8 alkynyl, (4) Cyc4 or (5) C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted with Cyc4;

R¹⁴⁸-R¹⁵⁰ each independently represents (1) a hydrogen atom, (2) C1-8 alkyl, (3) C2-8 alkenyl, (4) C2-8 alkynyl, (5) Cyc4 or (6) C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted with Cyc4;

Cyc4 has the same meaning as Cyc1, and Cyc4 may be substituted with 1-5 of R¹⁴⁴;

R¹⁴⁴ has the same meaning as R⁵¹, or R³ and R⁴ are taken together to represent



wherein R¹⁹⁰ and R¹⁹¹ each independently represents (1) a hydrogen atom, (2) C1-8 alkyl, (3) C2-8 alkenyl, (4) C2-8 alkynyl, (5) -COOR¹²⁰, (6) -CONR¹²¹R¹²², (7) Cyc4 or (8) C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted with 1-5 substituent(s) selected from (a) halogen, (b) nitrile, (c) Cyc4, (d) -COOR¹²⁰, (e) -CONR¹²¹R¹²², (f) -OR¹²³, (g) -SR¹²⁴, (h) -NR¹²⁵R¹²⁶, (i) -NR¹²⁷COR¹²⁸, (j) -SO₂NR¹²⁹R¹³⁰, (k) -OCOR¹³¹, (l) -NR¹³²SO₂R¹³³, (m) -NR¹³⁴COOR¹³⁵, (n) -NR¹³⁶CONR¹³⁷R¹³⁸, (o) -S-SR¹³⁹, (p) -NHC(=NH)NHR¹⁴⁰, (q) keto, (r) -NR¹⁴⁵CONR¹⁴⁶COR¹⁴⁷ and (s) -N(SO₂R¹³³)₂;

R¹²⁰-R¹⁴⁰ and R¹⁴⁵-R¹⁴⁷ have the same meanings as described above;

R⁵ represents (1) a hydrogen atom, (2) C1-8 alkyl, (3) Cyc5 or (4) C1-8 alkyl substituted with Cyc5;

Cyc5 has the same meaning as Cyc1, and Cyc5 may be substituted with 1-5 of R¹⁵⁰;

R¹⁵⁰ has the same meaning as R⁵¹;

an N-oxide thereof, a salt thereof, or a prodrug thereof.

- 11. A medicament which comprises a function inhibitor of an effector cell comprising a CCR5 antagonist, in combination with one, two or more immunosuppressive drug(s).
- 12. The medicament according to claim 11, wherein the one, two or more immunosuppressive drug(s) are selected from the group of tacrolimus, cyclosporine, sirolimus, corticosteroid, azathioprine, mycophenolate mofetil, FTY-720 and cyclophosphamide.
- 13. A method for prevention and/or treatment of a disease caused by effector cell function, which comprises administering to a mammal an effective amount of a compound of formula (I)

$$R^{1}-N \xrightarrow{N} \xrightarrow{N} \xrightarrow{N} R^{3} \qquad (I)$$

$$O \qquad R^{5}$$

wherein all symbols have the same meanings as those defined in claim 10, an N-oxide thereof, a salt thereof, or a prodrug thereof.

14. Use of a compound of formula (I)

$$R^{1}-N$$

$$R^{2}$$

$$R^{3}$$

$$R^{4}$$

$$R^{5}$$

$$R^{5}$$

$$R^{5}$$

wherein all symbols have the same meanings as those defined in claim 10,

an N-oxide thereof, a salt thereof, or a prodrug thereof for the manufacture of an agent for prevention and/or treatment of a disease caused by effector cell function.